ORIGINAL RESEARCH

Incidence, Predictors, and Clinical Impact of Early Prasugrel Cessation in Patients With ST-Elevation Myocardial Infarction

Konstantinos C. Koskinas, MD, MSc;* Thomas Zanchin, MD;* Roland Klingenberg, MD; Baris Gencer, MD; Fabrice Temperli, BA; Andreas Baumbach, MD; Marco Roffi, MD; Aris Moschovitis, MD; Oliver Muller, MD, PhD; David Tüller, MD; Stefan Stortecky, MD; Francois Mach, MD; Thomas F. Lüscher, MD; Christian M. Matter, MD; Thomas Pilgrim, MD; Dik Heg, MD; Stephan Windecker, MD; Lorenz Räber, MD, PhD

***Background*—**Early withdrawal of recommended antiplatelet treatment with clopidogrel adversely affects prognosis following percutaneous coronary interventions. Optimal antiplatelet treatment is essential following ST-segment elevation myocardial infarction (STEMI) given the increased risk of thrombotic complications. This study assessed the frequency, predictors, and clinical impact of early prasugrel cessation in patients with STEMI undergoing primary percutaneous coronary interventions.

***Methods and Results*—**We pooled patients with STEMI discharged on prasugrel in 2 prospective registries (Bern PCI Registry [NCT02241291] and SPUM-ACS (Inflammation and Acute Coronary Syndromes) [NCT01000701]) and 1 STEMI trial (COMFORTABLE-AMI (Comparison of Biomatrix Versus Gazelle in ST-Elevation Myocardial Infarction) [NCT00962416]). Prasugrel treatment status at 1 year was categorized as no cessation; crossover to another $P2Y_{12}$-inhibitor; physician-recommended discontinuation; and disruption because of bleeding, side effects, or patient noncompliance. In time-dependent analyses, we assessed the impact of prasugrel cessation on the primary end point, a composite of cardiac death, myocardial infarction, and stroke. Of all 1830 included patients (17% women, mean age 59 years), 83% were treated with new-generation drug-eluting stents. At 1 year, any prasugrel cessation had occurred in 13.8% of patients including crossover (7.2%), discontinuation (3.7%), and disruption (2.9%). Independent predictors of any prasugrel cessation included female sex, age, and history of cerebrovascular event. The primary end point occurred in 5.2% of patients and was more frequent following disruption (hazard ratio 3.04, 95% confidence interval,1.34–6.91; P=0.008), without significant impact of crossover or discontinuation. Consistent findings were observed for all-cause death, myocardial infarction, and stent thrombosis following prasugrel disruption.

***Conclusions*—**In this contemporary study of patients with STEMI, early prasugrel cessation was not uncommon and primarily involved change to another $P2Y_{12}$-inhibitor. Disruption was the only type of early prasugrel cessation associated with statistically significant excess in ischemic risk within 1 year following primary percutaneous coronary interventions. **(*J Am Heart Assoc*. 2018;7:e008085. DOI: 10.1161/JAHA.117.008085.)**

Key Words: antiplatelet therapy • coronary artery disease • myocardial infarction • prasugrel • prognosis

Flow restoration in the infarct-related artery by means of percutaneous coronary intervention (PCI) and dual antiplatelet therapy (DAPT) for potent platelet inhibition are the cornerstones for management of patients with acute ST-segment–elevation myocardial infarction (STEMI).[1,2] Compared with clopidogrel, prasugrel provides rapid-onset, more potent and consistent inhibition of platelet aggregation,[3] and reduces the risk of cardiovascular mortality and

From the Department of Cardiology, Bern University Hospital, Bern, Switzerland (K.C.K., T.Z., F.T., A.M., S.S., T.P., S.W., L.R.); Department of Cardiology, University Heart Center, University Hospital Zurich, Switzerland (R.K., T.F.L., C.M.M.); Division of Cardiology, Geneva University Hospital, Geneva, Switzerland (B.G., M.R., F.M.); Barts Heart Center, London, United Kingdom (A.B.); Service of Cardiology, Lausanne University Hospital, Lausanne, Switzerland (O.M.); Department of Cardiology, Triemlispital, Zurich, Switzerland (D.T.); CTU Bern and Institute of Social and Preventive Medicine (ISPM), University of Bern, Switzerland (D.H.).

Accompanying Data S1, Tables S1 through S7, and Figures S1, S2 are available at http://jaha.ahajournals.org/content/7/8/e008085/DC1/embed/inline-supplementary-material-1.pdf

*Dr Koskinas and Dr Zanchin contributed equally to this work.

Correspondence to: Lorenz Räber, MD, PhD, Department of Cardiology, Bern University Hospital, 3010 Bern, Switzerland. E-mail: lorenz.raeber@insel.ch

Received November 10, 2017; accepted March 21, 2018.

Clinical Perspective

What Is New?

- In a contemporary population of patients treated with primary percutaneous coronary intervention, early (before 1 year) cessation of prasugrel treatment was not uncommon and more frequently consisted of switching to clopidogrel.
- Early prasugrel cessation was associated with significantly increased risk of downstream ischemic events only in the context of disruption (ie, premature cessation because of bleeding, side effects, or patient noncompliance).

What Are the Clinical Implications?

- The increased risk of subsequent ischemic events should be considered when prasugrel is stopped early because of a bleeding event or noncompliance.
- Future studies should explore whether shorter than currently recommended duration of prasugrel treatment might be an acceptable option in properly selected patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention.

stent thrombosis in patients with myocardial infarction (MI).[4] Prasugrel is recommended over clopidogrel following primary PCI[1,2] and is used increasingly in real-world clinical practice.[5]

Nonadherence to recommended antiplatelet therapy following PCI is not uncommon and increases the risk of adverse ischemic events.[6–8] Notably, different modes of DAPT cessation (either driven by physician recommendation, patient noncompliance, or interventions necessitating temporary treatment withdrawal) appear to have varying effects on patient outcomes.[6] Previous studies assessing premature cessation of antiplatelet therapy focused primarily on more stable clinical settings and clopidogrel rather than novel, potent $P2Y_{12}$-inhibitors, and they often did not account for the temporal relation between treatment cessation and subsequent outcomes.[9,10] While STEMI is characterized by elevated ischemic risk compared with stable coronary artery disease (CAD) and is an independent predictor of stent thrombosis,[11] there are limited data on the adherence to guideline-recommended antiplatelet treatment following primary PCI. Moreover, although certain aspects of prasugrel treatment might adversely affect long-term compliance, including greater treatment cost or accentuated risk of bleeding, little is known about adherence to prasugrel in patients with STEMI. Against this background, we sought to address the incidence, underlying reasons, and clinical impact of early prasugrel cessation in a sizable, contemporary cohort of patients with STEMI treated by current standards (ie, primary PCI with predominantly new-generation drug-eluting stents [DES]).

Methods

The data, analytic methods, and study materials cannot be made available to other researchers for purposes of reproducing the results or replicating the procedure, given constraints in broader sharing of the data.

Patient Population

For the present study, we pooled patients with STEMI with the same qualifying diagnostic criteria who were included in the prospective Bern PCI Registry (NCT02241291), SPUM-ACS (Inflammation and Acute Coronary Syndromes) registry (NCT01000701), or COMFORTABLE-AMI (Comparison of Biomatrix Versus Gazelle in ST-Elevation Myocardial Infarction (STEMI)) trial (NCT00962416); were treated by means of PCI; and discharged on prasugrel. Details are presented in Data S1. Briefly, all patients undergoing PCI at Bern University Hospital, Switzerland as of 2009 have been prospectively entered into the Bern PCI Registry.[12,13] There are no formal exclusion criteria, and all patients providing informed consent for prospective follow-up are included. The SPUM-ACS cohort study is a multicenter, observational cohort study of patients presenting with acute coronary syndromes (ACS) at 4 Swiss tertiary centers with minimal exclusion criteria (severe physical disability, inability to comprehend study requirements, and estimated life expectancy <1 year).[14] The COMFORTABLE AMI trial was a multicenter, randomized controlled trial (RCT) comparing a biodegradable polymer–based biolimus-eluting stent with a bare-metal stent for primary PCI. Main exclusion criteria were mechanical complications of acute MI, use of vitamin-K antagonists, planned surgery (unless uninterrupted DAPT during the perisurgical period was judged feasible), and history of bleeding diathesis.[15] The studies complied with the Declaration of Helsinki and were approved by local institutional ethics committees. All patients provided written, informed consent.

Procedures

PCI was performed in accordance with current practice guidelines.[2] Thrombus aspiration was recommended in all patients whenever deemed technically feasible (COMFORTABLE-AMI) or whenever thrombus was angiographically visible (registry patients). In the COMFORTABLE-AMI trial, patients were randomly assigned to treatment with biolimus-eluting stents (BioMatrix, Biosensors Europe SA, Morges, Switzerland) or bare-metal stent (Gazelle, Biosensors Europe SA). In registry patients, the use of a newer-generation DES was recommended with final selection of stent type left at the discretion of the operator. Periprocedural management,

including dose of unfractionated heparin or use of glycoprotein IIb/IIIa inhibitors, was left to the operators' discretion. DAPT consisting of aspirin and a $P2Y_{12}$-inhibitor was initiated before, at the time of, or immediately after the procedure. The recommended treatment duration was 1 year for prasugrel and lifelong treatment for aspirin for both RCT and registry patients. Prasugrel administration was discouraged in patients with prior cerebrovascular events. Recommended maintenance dose for prasugrel was 10 mg, or 5 mg in patients with age >75 years or body weight <60 kg.

Patient Follow-Up

Patients were prospectively followed throughout 1 year after PCI to assess adverse cardiac and cerebrovascular events in all 3 studies. Survival data were obtained from hospital records and municipal civil registries. A health questionnaire was sent to all living patients with questions on rehospitalization, medical treatment, and adverse events, followed by telephone contact in case of missing response. General practitioners, referring cardiologists, and patients were contacted, and external medical records, discharge letters, and coronary angiography documentation were systematically reviewed for additional information in case of potential events or any change in $P2Y_{12}$-inhibitor therapy. Independent study monitors verified source data according to a prespecified monitoring plan. Identical case record forms were used for all patients in the 2 registries as well as the RCT, and all data were stored in the same central database (Cardiobase, 2mT, Ulm, Germany). Medical treatment was recorded during index PCI, at discharge, and at 1 year. Adherence to prasugrel, date, and patient-reported reasons for cessation were specifically assessed via telephone interview or clinical visit at 1 year; in addition, all medical reports were screened for medication status. Because protocol-recommended duration of $P2Y_{12}$-inhibitor treatment was ≈1 year (unless recurrent ischemic events triggered longer continuation), we considered 330 days or more of treatment as adherence.

Adjudication of cessation events was done centrally for all patients included in the pooled data set. Prespecified categories of prasugrel treatment status at 1 year included no cessation (continuous 1-year treatment) or cessation (any stop before 1 year). Cessation was classified as (1) crossover to another $P2Y_{12}$-inhibitor (clopidogrel or ticagrelor); (2) physician-recommended discontinuation (because of initiation of oral anticoagulation, surgery/intervention, or unspecified physician decision); and (3) disruption because of bleeding, perceived side effects, or patient noncompliance. Discontinuation and disruption were defined similarly to the PARIS (Patterns of Non-Adherence to Antiplatelet Regimens in Stented Patients) study.[6] Because of the potential for de-escalation from prasugrel to a less-potent antiplatelet agent, we also recorded crossover that was not reported in PARIS (which included 92% clopidogrel-treated patients). Moreover, because timing of possible re-initiation of prasugrel was not captured in this population, we were unable to define interruptions (defined as cessation for up to 14 days because of surgery in PARIS); temporary cessations because of surgery or other interventions were included under physician-decided discontinuation in our analysis. First cessation events are reported, such that some patients with cessation were receiving prasugrel at 1 year because of subsequent re-initiation.

Clinical End Points and Study Assessments

Clinical events were adjudicated by an independent clinical events committee for each study. Because 1 center (Bern University Hospital, Bern, Switzerland) had the leading role for planning, coordination, and execution of all 3 studies, outcome definitions were identical and event adjudication was done in a consistent, comparable manner for all patients included in the 3 studies. Cardiac death was defined as any death from an immediate cardiac cause, procedure-related mortality, and death of unknown cause. Definitions of spontaneous and periprocedural MI are detailed in Data S1. Stent thrombosis was defined according to the Academic Research Consortium definitions.[16] Bleeding was categorized according to Bleeding Academic Research Consortium as well as Thrombolysis in Myocardial Infarction criteria.[17] For the present analysis, the primary end point was a composite of cardiac death, nonfatal MI, and stroke. The key secondary end point was the composite of cardiac death, MI, stroke, target-vessel revascularization, and definite or probable stent thrombosis.

Statistical Analyses

Continuous variables are summarized as mean±SD and categorical ones as numbers (percentages). *P* values for between-group comparisons are based on *t* tests, Fisher exact tests, and χ^2 tests as appropriate. Lesion characteristics were compared using mixed linear, logistic, and multinomial regression models accounting for multiple lesions per patient. Kaplan–Meier curves were constructed for time to prasugrel cessation. Predictors of early prasugrel cessation were modeled using Cox models and those predictors with significant relationship ($P<0.2$) were evaluated for inclusion into a multivariate model; predictors with $P<0.15$ inside the multivariable model were finally retained. Using Cox models with time-varying covariates, we examined the effect of prasugrel cessation on clinical outcomes. For patients with any of the 3 types of early cessation (discontinuation,

crossover, or disruption), the follow-up time was split into 2 periods, before versus after the first recorded given type of cessation; events occurring in patients without cessation or before treatment cessation were used as reference, and no other covariates were included. Results are presented as hazard ratios (HR) with corresponding 95% confidence intervals (CI). For all clinical events, expected numbers were calculated as number of events divided by the HR (compared with the reference of being on prasugrel treatment). Analyses were performed in Stata 14.2.

Results

Baseline Characteristics

Of all 4454 patients with STEMI enrolled between October 2009 and June 2014, 1953 were discharged on prasugrel and 1830 patients were finally included in the present analysis (Figure 1). Clinical follow-up at 1-year post-PCI was available for all but 3 patients (Table S1). Within 1 year, any cessation of prasugrel had occurred in 252 patients (13.8%). Patterns of cessation included crossover (7.2%), physician-recommended discontinuation (3.7%), and disruption (2.9%). Crossover included switching primarily to clopidogrel or, less frequently, ticagrelor (83.1% versus 8.5% of patients in the crossover group were on clopidogrel versus ticagrelor at 1 year, respectively; Table S2). The time course of different types of prasugrel cessation is summarized in Figure 2, indicating earlier crossover versus more delayed discontinuation or disruption (median time with 25% to 75% interquartile range 31 [10–115] versus 207 [120–291] versus 158 [62–250] days, respectively).

Baseline characteristics are summarized in Table 1. Compared with patients with no early cessation, those with crossover to clopidogrel or ticagrelor were older, more frequently female with a history of cerebrovascular event, and less frequently had insulin-treated diabetes mellitus. Moreover, history of malignancy and anemia were more

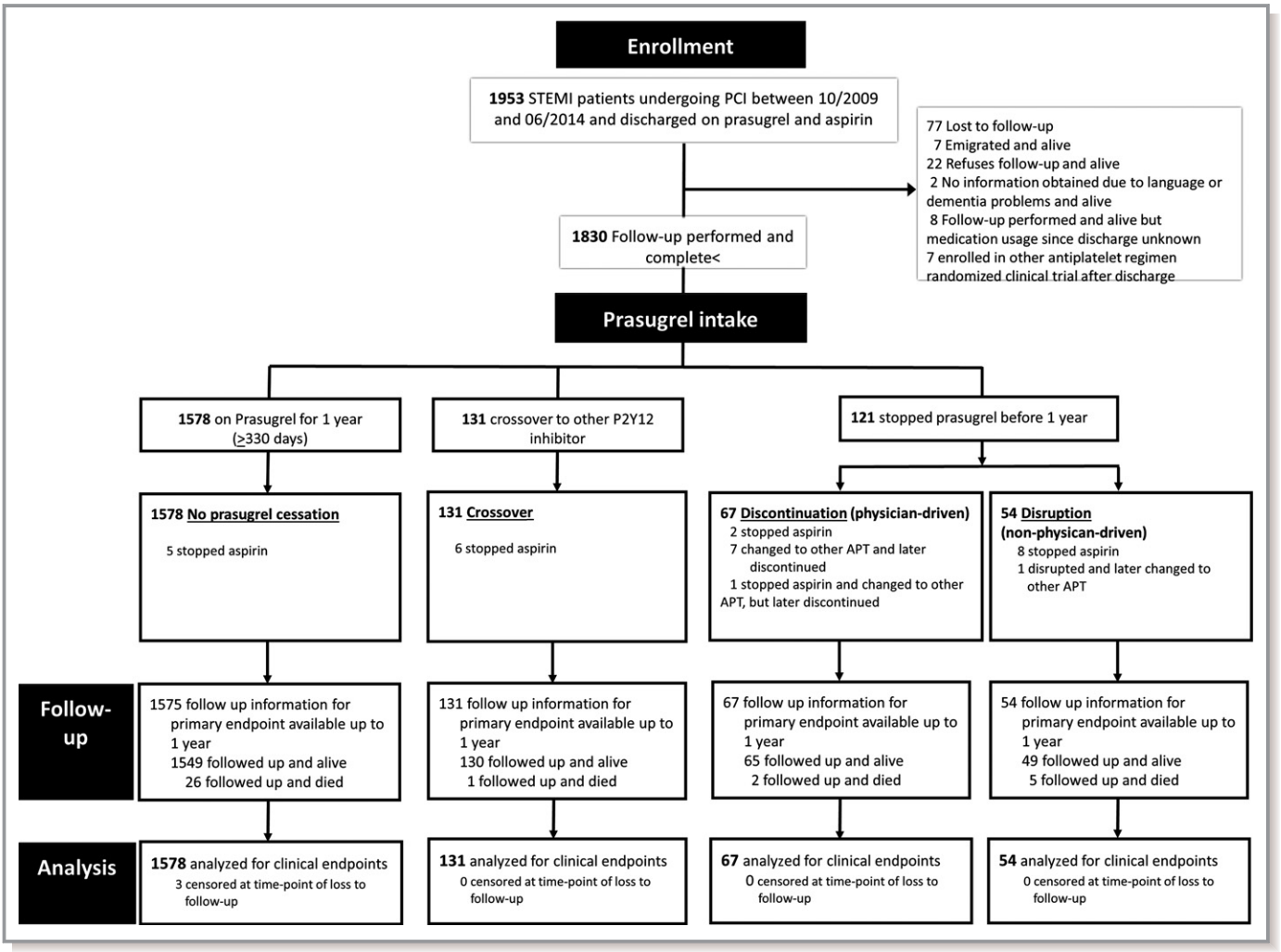


Figure 1. Summary of study flow. APT indicates antiplatelet therapy; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction.

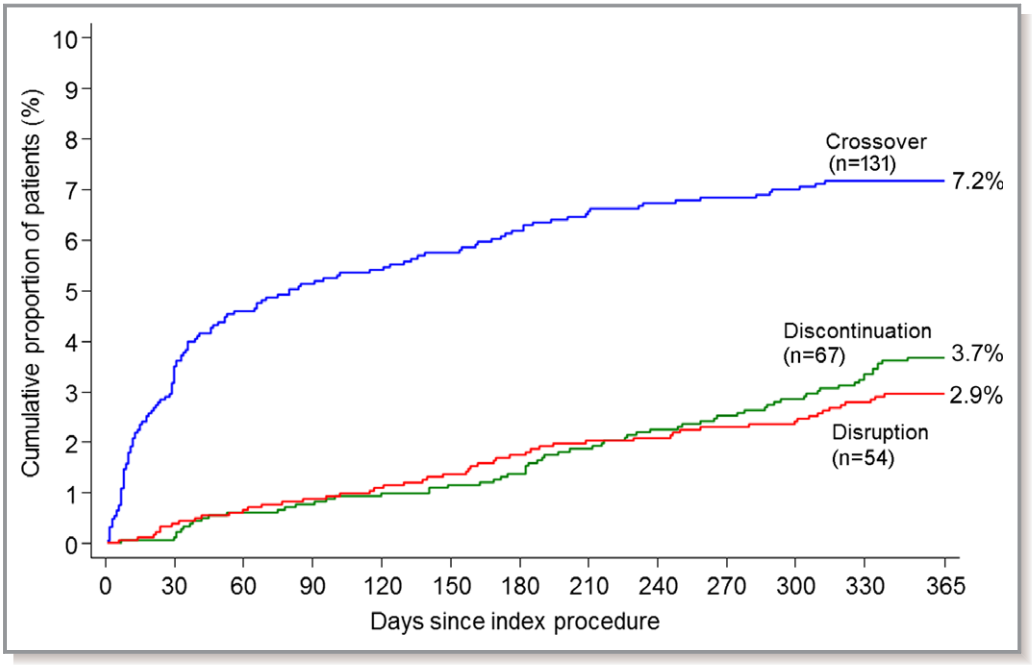


Figure 2. One-year Kaplan–Meier plots of crossover, physician-recommended discontinuation, and disruption of prasugrel throughout 1 year.

frequent in patients with discontinuation. We found no substantive differences with respect to professional background, marital status, and educational level (Table S3). Patients with crossover were more commonly treated with new-generation DES and less frequently with bare-metal stent (Table 2). Independent predictors of any early cessation included female sex, history of cerebrovascular event, and age (Table 3 and Table S4).

Reasons for Prasugrel Cessation

Patient-reported reasons for early prasugrel cessation are illustrated in Figure 3. Leading reasons for crossover included unspecified reason, oral anticoagulation initiation, bleeding, interventions, and perceived side effects. Reasons for discontinuation were unspecified physician recommendation, oral anticoagulation initiation, and interventions. Leading reasons for disruption were patient preference, bleeding, side effects, and treatment cost (Figure 3).

Clinical Outcomes in Relation to Early Prasugrel Cessation

At 1 year, the primary end point had occurred in 95 patients (5.2%) (Table 4). Figure 4 summarizes 1-year clinical outcomes in patients without cessation (reference) compared with events occurring after any type of early prasugrel cessation. The primary end point occurred more frequently following disruption (HR: 3.04, 95% CI, 1.34–6.91; P=0.008). Differences were consistent for the key secondary end point (HR: 2.39, 95% CI, 1.12–5.10; P=0.03), all-cause death (HR: 8.08, 95% CI, 3.05–21.37; P<0.001), cardiac death (HR: 7.35, 95% CI, 2.48–21.80; P<0.001), MI (HR: 4.00, 95% CI, 1.61–9.94; P=0.003), and definite or probable stent thrombosis (HR: 2.96, 95% CI, 1.08–8.12; P=0.03). No significant differences were observed following discontinuation or crossover for the primary or secondary end points. There was no association between early treatment cessation and subsequent bleeding events (Figure S1). Table S5 summarizes individual primary end point events following any mode of early prasugrel cessation. Median time from prasugrel cessation to first primary end point event was 10 days following crossover, 35 days following discontinuation, and 8 days following disruption.

Sensitivity Analyses: RCT Versus Registry Patients

Patients enrolled in the RCT (n=484, 26.4%) had a lower rate of prior PCI and less frequently presented with Killip class IV, with otherwise nondiffering baseline characteristics compared with patients enrolled in the registries (n=1346, 73.6%) (Table S6). The frequency of overall vprasugrel cessation as well as of each type of cessation did not differ significantly between patients enrolled in the RCT versus the registries (Table S7). Consistent with the findings in the entire pooled population, disruption, but not crossover or discontinuation, was associated with higher risk of the primary and secondary

Table 1. Baseline Clinical Characteristics

	No Cessation (n=1578)	Crossover (n=131)	Discontinuation (n=67)	Disruption (n=54)	*P* Value (vs No Cessation)		
					Crossover	Discontinuation	Disruption
Age	58.9±10.7	61.2±11.5	60.9±13.3	59.9±11.7	0.02	0.14	0.49
Female sex	247 (15.7)	38 (29.0)	20 (29.9)	7 (13)	<0.001	0.004	0.71
BMI	27.4±4.2	26.8±4.0	26.3±4.4	27.2±4.3	0.11	0.04	0.66
Current smoking	748 (48.0)	58 (44.3)	28 (43.8)	28 (52.8)	0.47	0.53	0.58
Hyperlipidemia	799 (51.1)	75 (57.3)	36 (53.7)	25 (47.2)	0.20	0.71	0.58
Hypertension	733 (46.6)	65 (49.6)	23 (34.3)	19 (35.2)	0.52	0.06	0.13
Diabetes mellitus	212 (13.5)	11 (8.4)	6 (9)	6 (11.1)	0.11	0.36	0.84
Insulin-dependent	50 (3.2)	0 (0)	2 (3.0)	2 (3.7)	0.03	1.00	0.69
Family history of CAD	403 (25.9)	37 (28.5)	14 (20.9)	8 (15.1)	0.53	0.39	0.08
Renal dysfunction*	113 (8.1)	12 (10.4)	7 (10.9)	3 (6.3)	0.38	0.36	1.00
Peripheral artery disease	35 (2.2)	2 (1.5)	0 (0)	1 (1.9)	1.00	0.40	1.00
History of cerebrovascular event	9 (0.6)	4 (3.1)	1 (1.5)	0 (0)	0.01	0.34	1.00
Previous PCI	135 (8.6)	11 (8.4)	2 (3.0)	3 (5.6)	1.00	0.12	0.62
Previous CABG	27 (1.7)	1 (0.8)	0 (0.0)	0 (0)	0.72	0.62	1.00
Time from symptom onset to balloon inflation (min)	226 (159; 385)	244 (157; 465)	259 (165; 562)	228 (156; 377)	0.38	0.09	0.95
Killip class IV at presentation	76 (4.8)	8 (6.2)	3 (4.5)	0 (0)	0.52	1.00	0.18
LVEF (%)	48.0±11.1	46.4±11.6	44.4±12.0	51.1±9.2	0.16	0.02	0.06
History of malignancy	66 (4.2)	0 (0)	10 (14.9)	4 (7.4)	0.008	0.001	0.29
Anemia†	162 (12.3)	13 (11.7)	12 (21.1)	1 (2.4)	1.00	0.06	0.05
Thrombocytopenia‡	32 (2.4)	1 (0.9)	1 (1.8)	1 (2.4)	0.51	1.00	1.00

Data are summarized as mean±SD, median (25–75% interquartile range), or count (%). BMI indicates body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.
*Defined as estimated glomerular filtration rate <60 mL/min per 1.73 m² using the Cockcroft-Gault formula.
†Hemoglobin <130 g/L for men or <120 g/L for women.
‡Thrombocytes <150 g/L.

end points, MI, all-cause and cardiac mortality at 1 year in a sensitivity analysis focusing only on patients included in the registries (Figure S2).

Discussion

While current recommendations advocate DAPT for 1 year following acute MI, there is limited evidence regarding adherence to prasugrel—one of the preferred antiplatelet agents in this context. This study assessed the incidence, reasons, and clinical impact of early prasugrel cessation in a sizable, contemporary cohort of patients with STEMI treated with PCI by current standards. Prasugrel cessation before 1 year was not uncommon (≈14%), but was less frequent compared with previous studies focusing on any DAPT cessation post-PCI in more stable clinical settings.[6–10] Crossover to another $P2Y_{12}$-inhibitor, mainly clopidogrel, was more frequent compared with physician-recommended discontinuation or disruption (because of bleeding, side effects, or noncompliance). Clinical characteristics previously linked to higher bleeding risk[18] were more common in patients who stopped prasugrel, suggesting that concerns about bleeding likely influenced decision-making regarding antiplatelet management. Even though the rate of major adverse cardiac events was numerically higher following discontinuation, disruption was the only mode of early prasugrel cessation associated with a statistically significant adverse impact on subsequent cardiovascular outcomes.

Rapid mechanical reperfusion with coronary stenting and potent adjunctive antithrombotic treatment are the principles for optimal management of patients with STEMI. Prasugrel, a potent and rapid-acting thienopyridine, is more effective than clopidogrel for prevention of ischemic events in patients with MI including those with STEMI.[4,19] Current guidelines recommend 12-month DAPT consisting of aspirin and a $P2Y_{12}$-inhibitor, preferably prasugrel or ticagrelor unless contraindicated.[1,2] In this study, 86% of patients with STEMI remained on continuous prasugrel treatment within 1 year

Table 2. Procedural Characteristics

	No Cessation (n=1578)	Crossover (n=131)	Discontinuation (n=67)	Disruption (n=54)	*P* Value (vs No Cessation)		
					Crossover	Discontinuation	Disruption
Number of lesions	2219	189	99	82			
Lesions treated per patient	1.41±0.73	1.44±0.81	1.48±0.81	1.52±0.77	0.59	0.40	0.27
Multivessel treatment	174 (11.)	17 (13)	10 (15.2)	8 (14.8)	0.47	0.32	0.38
Treated vessels							
Left main coronary artery	28 (1.8)	3 (2.3)	0 (0)	0 (0)	0.73	0.62	1.00
Left anterior descending artery	748 (47.5)	66 (50.4)	39 (59.1)	27 (50)	0.53	0.08	0.78
Left circumflex artery	301 (19.1)	22 (16.8)	13 (19.7)	6 (11.1)	0.56	0.87	0.16
Right coronary artery	676 (42.9)	59 (45)	25 (37.9)	29 (53.7)	0.65	0.45	0.13
Saphenous vein graft	9 (0.6)	0 (0)	0 (0)	0 (0)	1.00	1.00	1.00
Number of stents per lesion	1.33±0.61	1.32±0.60	1.33±0.61	1.30±0.65	0.89	0.97	0.73
Type of stent per lesion*							
First-generation DES	27 (1.3)	1 (0.6)	0 (0)	0 (0)	0.42	0.62	0.62
New-generation DES	1740 (82.9)	158 (89.3)	62 (73.8)	62 (80.5)	0.04	0.09	0.65
BMS	339 (16.2)	17 (9.6)	22 (26.2)	16 (20.8)	0.03	0.05	0.36
Total stent length per lesion (mm)	27.2±14.6	29.1±16.1	25.3±12.9	26.2±12.5	0.10	0.27	0.57
Minimum stent diameter per lesion (mm)	3.05±0.52	3.04±0.51	3.03±0.51	3.05±0.48	0.84	0.97	0.96
Thrombus aspiration	890 (40.3)	75 (39.9)	34 (35.1)	31 (37.8)	0.93	0.33	0.68
Bifurcation lesion (any lesion)	229 (14.5)	22 (16.8)	11 (16.7)	8 (14.8)	0.52	0.60	1.00
Long lesion†	249 (23.6)	19 (23.8)	7 (16.7)	11 (28.9)	1.00	0.36	0.44

BMS indicates bare-metal stent; DES, drug-eluting stent.
*First-generation DES: Cypher, Endeavour. Totals for types of stent do not sum up to the number of total stents, because 7 lesions were treated with both new-generation DES and BMS.
†Any total stent length ≥20 mm.

following PCI. Considering that more than half of early prasugrel cessations involved switching to another $P2Y_{12}$-inhibitor and in conjunction with high adherence to aspirin, our findings show adherence to guideline-recommended DAPT duration in >90% of patients. This finding likely reflects appreciation of the persistently elevated ischemic risk following acute STEMI. Previous investigations reported higher rates of early DAPT cessation within 1 year post PCI, ranging between 18.5% and 24%,[6–10] but this needs to be interpreted in view of different study populations (primarily stable patients with CAD) and antiplatelet treatments (mostly clopidogrel) as well as varying definitions of treatment cessation across studies.

Table 3. Multivariate Predictors of Any Prasugrel Cessation

	n	HR (95% CI)	*P* Value
Female sex	1619	1.63 (1.20–2.23)	0.002
History of cerebrovascular event	1619	3.88 (1.44–10.46)	0.007
Age (per 10 y)	1619	1.15 (1.02–1.31)	0.024

CI indicates confidence interval; HR, hazard ratio.

Analyses of correlates and underlying reasons for prasugrel cessation provided additional important insights. Crossover to clopidogrel—the most common pattern of cessation—occurred more frequently among older, female patients with a history of malignancy or prior cerebrovascular event (ie, a formal contraindication for prasugrel). Age and female sex previously emerged as independent predictors of bleeding in prasugrel-treated patients.[18] Along these lines, it is important to note that the superior efficacy of prasugrel over clopidogrel for reduction of ischemic events was coupled with excess bleeding in the overall population,[4] but not in the prespecified STEMI subanalysis of the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction 38) trial.[19] The finding that oral anticoagulation initiation was a main reason for crossover or discontinuation is consistent with evidence of unacceptably high bleeding risk attributed to triple antithrombotic therapy including prasugrel.[20] Collectively these findings likely reflect physician consideration of bleeding risk factors that may have led to

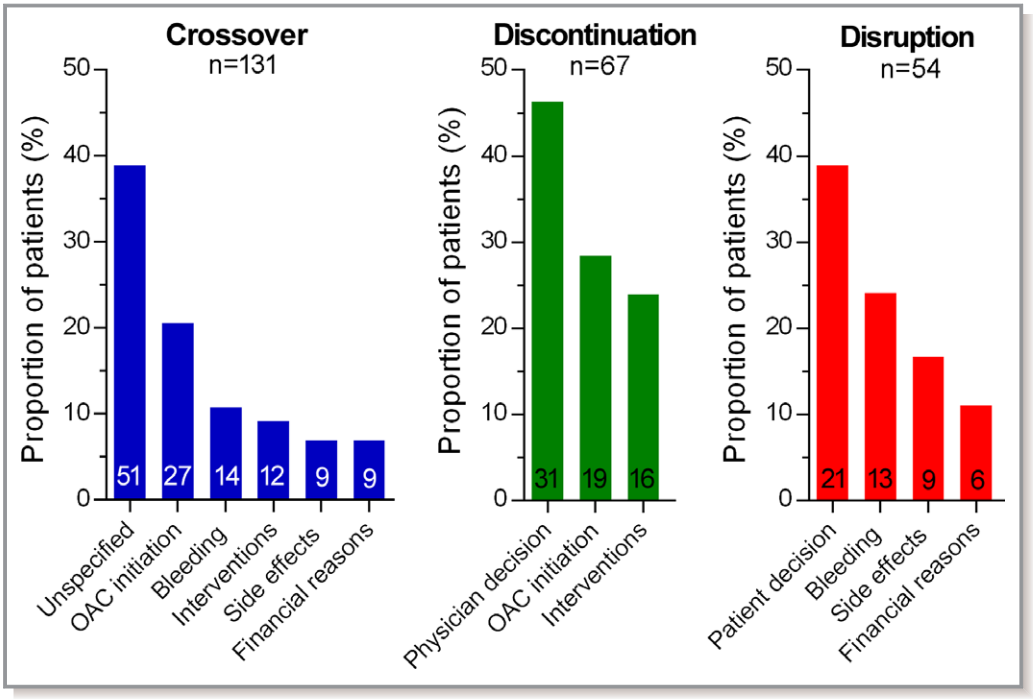


Figure 3. Patient-reported reasons for early prasugrel cessation (crossover, physician-recommended discontinuation, and disruption). OAC indicates oral anticoagulation.

change from prasugrel to a less-potent antiplatelet agent. Conversely, with the exception of insulin-treated diabetes mellitus, we did not observe a greater cluster of well-recognized "ischemic" risk factors (eg, smoking, prior MI or PCI, graft stenting, and disease complexity[21]) in patients who remained on prasugrel during 1 year.

Previous studies assessing clinical outcomes in relation to early DAPT cessation in more stable clinical settings have yielded conflicting results. Several reports found no adverse impact of DAPT interruptions after 30 days post PCI with new-generation DES[9,10]; these studies, however, pooled all DAPT interruptions between 30 days and 12 months, thereby not accounting for the possibly differing ischemic risk throughout the entire period following the first month post-PCI. Other studies applying time-dependent analyses reported higher risk of ischemic events following early DAPT cessation[7,8] and importantly showed that the clinical sequelae depend on the underlying reason and mode of cessation.[6] Our present findings extend these observations in the very high-risk setting of patients with STEMI by demonstrating a lack of association between prasugrel discontinuation or crossover and greater ischemic risk. In contrast, prasugrel disruption was associated with 3-fold higher risk of major ischemic adverse events and consistently higher rates of mortality and stent thrombosis. Although direct comparisons are hindered by differing end point definitions, the incremental risk of major ischemic events following prasugrel disruption in STEMI appears to be greater compared with the respective risk following DAPT disruption in stable CAD or ACS patients in the PARIS registry[6] (HR 2.97 in this study versus 1.5 in PARIS). Notwithstanding these associations disfavoring disruption, early prasugrel cessation (by any mode) accounted for only a small proportion of all ischemic events within the first year following STEMI, since >80% of these events occurred on prasugrel treatment.

The leading cause of prasugrel disruption was cessations because of unjustified patient decision (ie, noncompliance). We did not detect clinical characteristics that could allow early identification of these patients. In view of the adverse clinical impact of disruption, our findings emphasize the need to continuously promote patient education and enhance compliance with recommended antiplatelet treatment following STEMI. Moreover, the link between bleeding, prasugrel disruption, and increased risk of downstream ischemic events in this study substantiates the concept that bleeding complications adversely impact long-term PCI outcomes at least in part by triggering early withdrawal of recommended antiplatelet treatment.

Recent recommendations advocate 12-month adherence to the combination of aspirin plus a (preferably potent) $P2Y_{12}$-inhibitor following primary PCI, but indicate that earlier discontinuation may be considered in patients at high risk of bleeding.[22] While limited by the observational nature of the study and relatively small number of events, our findings lend support to these Class IIb recommendations (which were based on limited data) by showing no excess ischemic risk in

Table 4. Incidence of Adverse Clinical Events Within 1 Year

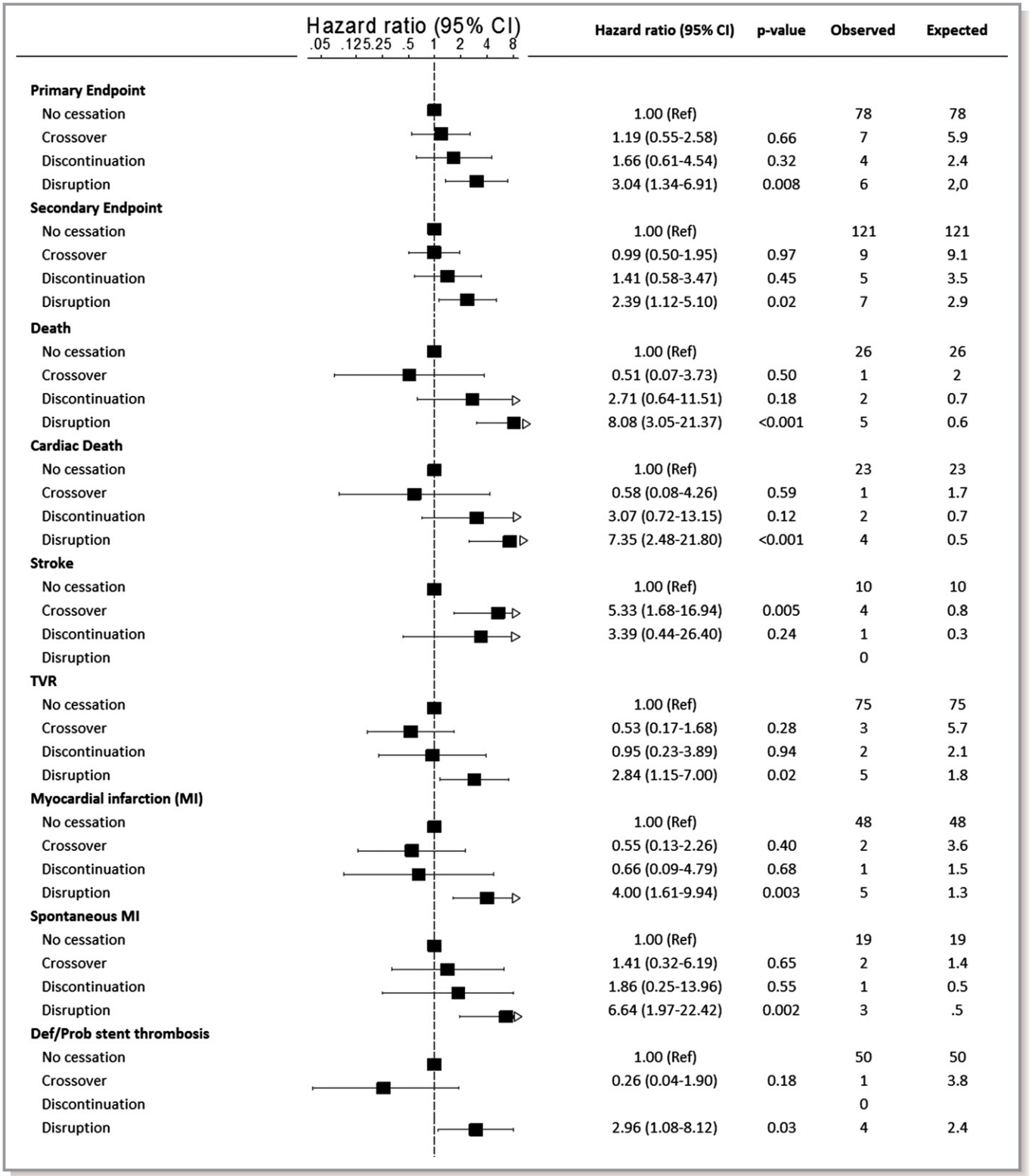
	No Cessation (n=1578)	Crossover (n=131)	Discontinuation (n=67)	Disruption (n=54)
Primary end point	65 (4.1)	13 (9.9)	9 (13.4)	8 (14.8)
Secondary end point	100 (6.3)	21 (16.1)	12 (17.9)	9 (16.7)
Death	26 (1.6)	1 (0.8)	2 (3.0)	5 (9.3)
Cardiac death	23 (1.5)	1 (0.8)	2 (3.0)	4 (7.5)
Myocardial infarction	40 (2.5)	8 (6.1)	3 (4.5)	5 (9.3)
Spontaneous MI	16 (1.0)	5 (3.8)	1 (1.5)	3 (5.7)
Death or MI	63 (4.0)	9 (6.9)	5 (7.6)	6 (10.9)
Stroke	5 (0.3)	4 (3.1)	4 (6)	2 (3.8)
TVR	63 (4.0)	10 (7.7)	7 (10.5)	5 (9.4)
Definite stent thrombosis	25 (1.6)	3 (2.3)	2 (3.0)	4 (7.6)
BARC 3 to 5 bleeding	41 (2.6)	14 (10.7)	5 (7.5)	6 (11.5)
BARC 3	40 (2.6)	11 (8.4)	4 (6)	6 (11.5)
BARC 4	0 (0.0)	3 (2.3)	1 (1.5)	0 (0.0)
BARC 5	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
TIMI major bleeding	21 (1.3)	11 (8.4)	3 (4.5)	5 (9.6)
TIMI minor bleeding	21 (1.3)	3 (2.3)	3 (4.5)	0 (0.0)

Counted are first events per event type per patient (% from Kaplan–Meier estimate). Cumulative incidence within 1 year following index PCI is presented, regardless of event occurrence before or following prasugrel cessation in patients with crossover, discontinuation, or disruption. Primary end point was a composite of cardiac death, nonfatal MI, and stroke. Secondary end point was a composite of cardiac death, MI, stroke, TVR, and definite or probable stent thrombosis. BARC indicates Bleeding Academic Research Consortium; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction; TVR, target vessel revascularization.

patients who discontinued prasugrel or changed to a less-potent agent based on justified medical decision (presumably related, at least in part, to higher bleeding risk). Along the same lines, a focused guideline update by the European Society of Cardiology recommended that in patients with ACS at high risk of bleeding, discontinuation of P2Y12-inhibitor therapy after 6 months post-stenting should be considered, as the risk of ischemic complication is highest immediately after the index event and then gradually declines.[23] These recommendations were based on studies including primarily non-ST segment elevation–ACS patients treated with clopidogrel,[24] and the need for further studies focusing on novel P2Y12 inhibitors was explicitly acknowledged.[23] Properly designed prospective studies are needed to assess tailored approaches for defining the potency and duration of antiplatelet therapy following STEMI, accounting for individual-patient bleeding and ischemic risk.

The TROPICAL ACS (Testing Responsiveness To Platelet Inhibition On Chronic Antiplatelet Treatment For Acute Coronary Syndromes) randomized trial recently showed that platelet function-guided de-escalation of prasugrel to clopidogrel 14 days after hospital discharge was noninferior to 1-year treatment with prasugrel in terms of net clinical benefit in patients with ACS.[25] In the TOPIC (Timing of Platelet Inhibition After Acute Coronary Syndrome) randomized study (including 646 ACS patients, 40% with STEMI), de-escalation of prasugrel or ticagrelor to clopidogrel 1 month post index event was superior to 1-year treatment with a potent agent for prevention of bleeding complications, without increase in ischemic events.[26] In the present observational analysis, we found no increase in ischemic events following crossover (including primarily de-escalation to clopidogrel and occurring at a median of 31 days post index PCI) compared with continued prasugrel treatment throughout 1 year.

The TRANSLATE-ACS registry reported early cessation of clopidogrel or prasugrel in 21% of STEMI or NSTE-ACS patients within 1-year post PCI.[27] Notably, that registry did not capture crossover, although this is not uncommon in clinical practice among patients treated with potent antiplatelet agents and was in fact the most common mode of prasugrel cessation in our analysis. Thienopyridine cessation (not including crossover) was substantially more common in TRANSLATE ACS compared with the present study (21% versus 6.3%, ie, the sum of discontinuation and disruption in our study). Whether this difference might reflect variations in practice patterns in the United States versus Europe (as suggested, for example, by considerable differences in the use of bare-metal stent versus DES in the 2 studies) or relate to more contemporary treatment patterns in the present analysis (enrollment extended up to 2014 versus 2012 in



	Hazard ratio (95% CI)	p-value	Observed	Expected
Primary Endpoint				
No cessation	1.00 (Ref)		78	78
Crossover	1.19 (0.55-2.58)	0.66	7	5.9
Discontinuation	1.66 (0.61-4.54)	0.32	4	2.4
Disruption	3.04 (1.34-6.91)	0.008	6	2,0
Secondary Endpoint				
No cessation	1.00 (Ref)		121	121
Crossover	0.99 (0.50-1.95)	0.97	9	9.1
Discontinuation	1.41 (0.58-3.47)	0.45	5	3.5
Disruption	2.39 (1.12-5.10)	0.02	7	2.9
Death				
No cessation	1.00 (Ref)		26	26
Crossover	0.51 (0.07-3.73)	0.50	1	2
Discontinuation	2.71 (0.64-11.51)	0.18	2	0.7
Disruption	8.08 (3.05-21.37)	<0.001	5	0.6
Cardiac Death				
No cessation	1.00 (Ref)		23	23
Crossover	0.58 (0.08-4.26)	0.59	1	1.7
Discontinuation	3.07 (0.72-13.15)	0.12	2	0.7
Disruption	7.35 (2.48-21.80)	<0.001	4	0.5
Stroke				
No cessation	1.00 (Ref)		10	10
Crossover	5.33 (1.68-16.94)	0.005	4	0.8
Discontinuation	3.39 (0.44-26.40)	0.24	1	0.3
Disruption			0	
TVR				
No cessation	1.00 (Ref)		75	75
Crossover	0.53 (0.17-1.68)	0.28	3	5.7
Discontinuation	0.95 (0.23-3.89)	0.94	2	2.1
Disruption	2.84 (1.15-7.00)	0.02	5	1.8
Myocardial infarction (MI)				
No cessation	1.00 (Ref)		48	48
Crossover	0.55 (0.13-2.26)	0.40	2	3.6
Discontinuation	0.66 (0.09-4.79)	0.68	1	1.5
Disruption	4.00 (1.61-9.94)	0.003	5	1.3
Spontaneous MI				
No cessation	1.00 (Ref)		19	19
Crossover	1.41 (0.32-6.19)	0.65	2	1.4
Discontinuation	1.86 (0.25-13.96)	0.55	1	0.5
Disruption	6.64 (1.97-22.42)	0.002	3	.5
Def/Prob stent thrombosis				
No cessation	1.00 (Ref)		50	50
Crossover	0.26 (0.04-1.90)	0.18	1	3.8
Discontinuation			0	
Disruption	2.96 (1.08-8.12)	0.03	4	2.4

Figure 4. Risk of clinical outcomes following early prasugrel cessation: crossover (n=131); discontinuation (n=67); and disruption (n=54). Results of time-dependent Cox model analyses for the risk of the primary and secondary end points. Presented are numbers of observed events (from Kaplan–Meier estimate), hazard ratios (HRs), and respective 95% confidence intervals (CI). The observed vs expected number of events are presented for each period, where expected numbers were calculated as number of events divided by the HR (compared with the reference of being on prasugrel treatment). The primary end point was a composite of cardiac death, nonfatal myocardial infarction (MI), and stroke. Secondary end point was a composite of cardiac death, MI, stroke, target-vessel revascularization (TVR), and definite or probable stent thrombosis.

TRANSLATE-ACS) cannot be definitively addressed. Of note, real-world observations indicate greater acceptance rates and a steady increase in the use of prasugrel over time.[5,28] Any thienopyridine cessation was associated with an increased risk of major adverse cardiac events in TRANSLATE ACS,[27] which contrast with our present findings in a STEMI cohort as well as the findings of the PARIS registry[6] in a broader PCI population.

This study has several limitations. First, the study was not designed to evaluate clinical outcomes in relation to prasugrel treatment; however, adverse events were prospectively defined outcome measures and were specifically evaluated during 1-year follow-up in all 3 studies, and adherence to medical treatment was assessed at predefined time-points applying standardized definitions. Second, the present cohort pooled patients from 2 prospective, all-comers registries and a randomized STEMI trial. However, the COMFORTABLE-AMI trial had a broadly inclusive design with minimal exclusion criteria; in addition, identical follow-up procedures and independent clinical event adjudication were applied in the randomized trial as in the registries, thereby minimizing patient heterogeneity in the present pooled cohort. Although some differences in study design and patient characteristics did exist, our sensitivity analyses focusing only on registry patients (Figure S2) showed consistent outcomes as in the entire pooled population. Despite the sizable STEMI cohort, this study may be underpowered to assess clinical outcomes in relation to different modes of prasugrel cessation; in particular, discontinuation was associated with a numerically (1.6-fold) higher risk of major adverse cardiac events, which nonetheless did not reach statistical significance, likely because of the small numbers of patients and limited numbers of events in each group. Unlike the PARIS study,[6] the exact timing of possible prasugrel reinitiation was not consistently captured in this study; therefore, temporary interruptions (eg, before surgery) could not be defined separately but were included under physician-determined discontinuation. While the association between prasugrel cessation and subsequent events is substantiated by being derived from time-varying analyses, the fact that no other covariates were considered is acknowledged as a limitation. Finally, the findings of this observational study are presented as hypothesis-generating only; prospective, adequately powered studies are required to assess outcomes in relation to shorter than currently recommended prasugrel treatment duration in the high-risk setting of STEMI.

Conclusions

Prasugrel cessation was observed in 1 of 7 patients with STEMI within 1 year following primary PCI in this contemporary study. Early cessation involved primarily change to another $P2Y_{12}$ inhibitor and was predicted by clinical characteristic portending higher bleeding risk. Prasugrel disruption (because of bleeding, side effects, or noncompliance) was associated with a statistically significant, 3-fold higher risk of major ischemic events.

Disclosures

SW has received research contracts to the institution (Department of Cardiology, Bern University Hospital - INSELSPITAL) from Abbott, Astra Zeneca, Boston Scientific, Biosensors, Biotronik, Cordis, Eli Lilly, Medtronic, and St Jude. LR has received research contracts to the institution from Abbott, Sanofi, and Regeneron and speaker fees from Amgen and Biotronik. DH is affiliated with CTU Bern, University of Bern, which has a staff policy of not accepting honoraria or consultancy fees but is involved in design, conduct, or analysis of clinical studies funded by not-for-profit and for-profit organizations. MR has received institutional unrestricted grants from Biotronik, Terumo, Boston Scientific, Medtronic, and Abbott Vascular and speakers fees from Cordis and Astra Zeneca. CMM has received research contracts to the institution from Abbott, Astra, Eli Lilly, Roche, and speaker fees from Amgen, Sanofi, Astra, Roche, and Eli Lilly. FM received honoraria from Amgen, AstraZeneca, BMS, Eli Lilly, MSD, Sanofi, and Pfizer. All other authors report that they have no relationships relevant to the contents of this article to disclose.

References

1. O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso JE, Tracy CM, Woo YJ, Zhao DX; CF/AHA Task Force. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;127:529–555.
2. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2014;35:2541–2619.
3. Michelson AD, Frelinger AL III, Braunwald E, Downey WE, Angiolillo DJ, Xenopoulos NP, Jakubowski JA, Li Y, Murphy SA, Qin J, McCabe CH, Antman EM, Wiviott SD. Pharmacodynamic assessment of platelet inhibition by prasugrel vs. clopidogrel in the TRITON-TIMI 38 trial. *Eur Heart J*. 2009;30:1753–1763.
4. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357:2001–2015.
5. Sandhu A, Seth M, Dixon S, Share D, Wohns D, Lalonde T, Moscucci M, Riba AL, Grossman M, Gurm HS. Contemporary use of prasugrel in clinical practice: insights from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium. *Circ Cardiovasc Qual Outcomes*. 2013;6:293–298.
6. Mehran R, Baber U, Steg PG, Ariti C, Weisz G, Witzenbichler B, Henry TD, Kini AS, Stuckey T, Cohen DJ, Berger PB, Iakovou I, Dangas G, Waksman R, Antoniucci D, Sartori S, Krucoff MW, Hermiller JB, Shawl F, Gibson CM, Chieffo A, Alu M, Moliterno DJ, Colombo A, Pocock S. Cessation of dual antiplatelet

treatment and cardiac events after percutaneous coronary intervention (PARIS). *Lancet*. 2013;382:1714–1722.

7. Cutlip DE, Kereiakes DJ, Mauri L, Stoler R, Dauerman HL. Thrombotic complications associated with early and late nonadherence to dual antiplatelet therapy. *JACC Cardiovasc Interv*. 2015;8:404–410.
8. Brar SS, Kim J, Brar SK, Zadegan R, Ree M, Liu IL, Mansukhani P, Aharonian V, Hyett R, Shen AY. Long-term outcomes by clopidogrel duration and stent type in a diabetic population with de novo coronary artery lesions. *J Am Coll Cardiol*. 2008;51:2220–2227.
9. Silber S, Kirtane AJ, Belardi JA, Liu M, Brar S, Rothman M, Windecker S. Lack of association between dual antiplatelet therapy use and stent thrombosis between 1 and 12 months following Resolute zotarolimus-eluting stent implantation. *Eur Heart J*. 2014;35:1949–1956.
10. Ferreira-Gonzalez I, Marsal JR, Ribera A, Permanyer-Miralda G, García-Del Blanco B, Martí G, Cascant P, Masotti-Centol M, Carrillo X, Mauri J, Batalla N, Larrousse E, Martín E, Serra A, Rumoroso JR, Ruiz-Salmerón R, de la Torre JM, Cequier A, Gómez-Hospital JA, Alfonso F, Martín-Yuste V, Sabatè M, García-Dorado D. Double antiplatelet therapy after drug-eluting stent implantation: risk associated with discontinuation within the first year. *J Am Coll Cardiol*. 2012;60:1333–1339.
11. Dangas GD, Caixeta A, Mehran R, Permanyer-Miralda G, García-Del Blanco B, Martí G, Cascant P, Masotti-Centol M, Carrillo X, Mauri J, Batalla N, Larrousse E, Martín E, Serra A, Rumoroso JR, Ruiz-Salmerón R, de la Torre JM, Cequier A, Gómez-Hospital JA, Alfonso F, Martín-Yuste V, Sabatè M, García-Dorado D. Frequency and predictors of stent thrombosis after percutaneous coronary intervention in acute myocardial infarction. *Circulation*. 2011;123:1745–1756.
12. Koskinas KC, Räber L, Zanchin T, Wenaweser P, Stortecky S, Moschovitis A, Khattab AA, Pilgrim T, Blöchlinger S, Moro C, Jüni P, Meier B, Heg D, Windecker S. Clinical impact of gastrointestinal bleeding in patients undergoing percutaneous coronary interventions. *Circ Cardiovasc Interv*. 2015;8:e002053.
13. Koskinas KC, Räber L, Zanchin T, Pilgrim T, Stortecky S, Hunziker L, Blöchlinger S, Billinger M, Gartwyl F, Moro C, Moschovitis A, Jüni P, Heg D, Windecker S. Duration of triple antithrombotic therapy and outcomes among patients undergoing percutaneous coronary intervention. *JACC Cardiovasc Interv*. 2016;9:1473–1483.
14. Räber L, Klingenberg R, Heg D, Kelbæk H, Roffi M, Tüller D, Baumbach A, Zanchin T, Carballo D, Ostojic M, Stefanini GG, Rodondi N, von Birgelen C, Moschovitis A, Engstrøm T, Gencer B, Auer R, Meier B, Mach F, Lüscher TF, Jüni P, Matter CM, Windecker S. Safety of Prasugrel loading doses in patients pre-loaded with Clopidogrel in the setting of primary percutaneous coronary intervention: results of a nonrandomized observational study. *JACC Cardiovasc Interv*. 2015;8:1064–1074.
15. Räber L, Kelbaek H, Ostojic M, Baumbach A, Heg D, Tüller D, von Birgelen C, Roffi M, Moschovitis A, Khattab AA, Wenaweser P, Bonvini R, Pedrazzini G, Kornowski R, Weber K, Trelle S, Lüscher TF, Taniwaki M, Matter CM, Meier B, Jüni P, Windecker S. Effect of biolimus-eluting stents with biodegradable polymer vs bare-metal stents on cardiovascular events among patients with acute myocardial infarction: the COMFORTABLE AMI randomized trial. *JAMA*. 2012;308:777–787.
16. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. 2007;115:2344–2351.
17. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, Serebruany V, Valgimigli M, Vranckx P, Taggart D, Sabik JF, Cutlip DE, Krucoff MW, Ohman EM, Steg PG, White H. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation*. 2011;123:2736–2747.
18. Hochholzer W, Wiviott SD, Antman EM, Contant CF, Guo J, Giugliano RP, Dalby AJ, Montalescot G, Braunwald E. Predictors of bleeding and time dependence of association of bleeding with mortality: insights from the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel—Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38). *Circulation*. 2011;123:2681–2689.
19. Montalescot G, Wiviott SD, Braunwald E, Contant CF, Guo J, Giugliano RP, Dalby AJ, Montalescot G, Braunwald E. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON TIMI 38): double-blind, randomised controlled trial. *Lancet*. 2009;373:723–731.
20. Sarafoff N, Martischnig A, Wealer J, Mayer K, Mehilli J, Sibbing D, Kastrati A. Triple therapy with aspirin, prasugrel, and vitamin K antagonists in patients with drug-eluting stent implantation and an indication for oral anticoagulation. *J Am Coll Cardiol*. 2013;61:2060–2066.
21. Yeh RW, Secemsky EA, Kereiakes DJ, Normand SL, Gershlick AH, Cohen DJ, Spertus JA, Steg PG, Cutlip DE, Rinaldi MJ, Camenzind E, Wijns W, Apruzzese PK, Song Y, Massaro JM, Mauri L. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. *JAMA*. 2016;315:1735–1749.
22. Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, Granger CB, Lange RA, Mack MJ, Mauri L, Mehran R, Mukherjee D, Newby LK, O'Gara PT, Sabatine MS, Smith PK, Smith SC Jr. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: an Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery. *Circulation*. 2016;134:e123–e155.
23. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, Jüni P, Kastrati A, Kolh P, Mauri L, Montalescot G, Neumann FJ, Petricevic M, Roffi M, Steg PG, Windecker S, Zamorano JL, Levine GN. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2018;39:213–260.
24. Palmerini T, Della Riva D, Benedetto U, Bacchi Reggiani L, Feres F, Abizaid A, Gilard M, Morice MC, Valgimigli M, Hong MK, Kim BK, Jang Y, Kim HS, Park KW, Colombo A, Chieffo A, Sangiorgi D, Biondi-Zoccai G, Généreux P, Angelini GD, Pufulete M, White J, Bhatt DL, Stone GW. Three, six, or twelve months of dual antiplatelet therapy after DES implantation in patients with or without acute coronary syndromes: an individual patient data pairwise and network meta-analysis of six randomized trials and 11 473 patients. *Eur Heart J*. 2017;38:1034–1043.
25. Sibbing D, Aradi D, Jacobshagen C, Gross L, Trenk D, Geisler T, Orban M, Hadamitzky M, Merkely B, Kiss RG, Komócsi A, Dézsi CA, Holdt L, Felix SB, Parma R, Klopotowski M, Schwinger RHG, Rieber J, Huber K, Neumann FJ, Koltowski L, Mehilli J, Huczek Z, Massberg S. Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomized open-label, multicentre trial. *Lancet*. 2017;390:1747–1757.
26. Cuisset T, Deharo P, Quilici J, Johnson TW, Deffarges S, Bassez C, Bonnet G, Fourcade L, Mouret JP, Lambert M, Verdier V, Morange PE, Alessi MC, Bonnet JL. Benefit of switching dual antiplatelet therapy after acute coronary syndrome: the TOPIC (timing of platelet inhibition after acute coronary syndrome) randomized study. *Eur Heart J*. 2017;38:3070–3078.
27. Fosbøl EL, Ju C, Anstrom KJ, Zettler ME, Messenger JC, Waksman R, Effron MB, Baker BA, Cohen DJ, Peterson ED, Wang TY. Early cessation of adenosine diphosphate receptor inhibitors among acute myocardial infarction patients treated with percutaneous coronary intervention: insights from the TRANSLATE-ACS Study. *Circ Cardiovasc Interv*. 2016;9:e003602.
28. Nordstrom BL, Simeone JC, Zhao Z, Molife C, McCollam PL, Ye X, Effron MB. Adherence and persistence with prasugrel following acute coronary syndrome with percutaneous coronary intervention. *Am J Cardiovasc Drugs*. 2013;13:263–271.

Supplemental Material

Data S1.

Supplemental Methods

Eligibility criteria for the Bern PCI Registry

All patients undergoing clinically indicated percutaneous coronary intervention (PCI) (for stable coronary artery disease, silent ischemia, ST-elevation myocardial infarction [STEMI], non-ST-elevation myocardial infarction [NSTEMI], or unstable angina [UA]) at Bern University Hospital, Switzerland as of January 2009 are prospectively entered into the ongoing Bern PCI Registry. There are no formal exclusion criteria, and all patients who provided informed consent were included in this registry (1-3).

Eligibility criteria for the SPUM ACS registry

Female and male patients aged 18 years and older presenting within 5 days (preferably 72 hours) after pain onset with the main diagnosis of STEMI, NSTEMI, or unstable angina were included in the registry (4,5). Included patients had symptoms compatible with angina pectoris (chest pain, dyspnea) and fulfilled at least one of the following criteria: (i.) persistent ST-segment elevation or depression, T inversion or dynamic ECG changes, new left bundle branch block; (ii.) evidence of positive troponin with rise and/or fall in serial troponin levels; (iii.) known coronary artery disease (specified as status after myocardial infarction, coronary artery bypass graft surgery, or PCI) or newly documented $\geq$ 50% stenosis of an epicardial coronary artery during the initial catheterization. Exclusion criteria were severe physical disability, inability to comprehend study, and estimated life expectancy less than 1 year (due to non-cardiac reasons).

The present analysis included all patients from the Bern PCI Registry and SPUM ACS cohort who were enrolled between October 2009 (clinical approval of prasugrel in Switzerland) and June 2014 with main diagnosis of STEMI and were discharged on prasugrel.

Eligibility criteria for the COMFORTABLE AMI trial

Consecutive patients aged 18 years or older with acute ST-segment elevation of at least 1 mm in two or more contiguous leads, true posterior myocardial infarction or new left bundle branch block

were eligible for randomization in the presence of at least one culprit lesion in the infarct vessel (6-8). Exclusion criteria were presence of mechanical complications of acute myocardial infarction, known allergy to any study medication, use of vitamin K-antagonists, planned surgery unless dual anti-platelet therapy could be maintained throughout the peri-surgical period, history of bleeding diathesis or known coagulopathy, pregnancy, participation in another trial before reaching the primary endpoint, inability to provide informed consent, and non-cardiac co-morbid conditions with life expectancy below 1 year.

Definition of myocardial infarction

The diagnosis of spontaneous (>48 hours post index event) Q-wave myocardial infarction required new pathological Q waves in two or more contiguous ECG leads. The diagnosis of spontaneous non-Q wave MI required documented biomarker elevations consisting of 1) CK-MB >1*URL, or 2) in the absence of CK-MB, standard troponin elevations >1*URL, or 3) in the absence of standard troponin high sensitivity troponin>1*URL. The appropriate enzyme data were considered in aggregate with clinical parameters suggesting evidence of myocardial ischemia based on symptoms, electrocardiographic changes, cardiac imaging findings or new regional wall motion abnormalities.

Peri-procedural myocardial infarction was adjudicated according to three scenarios as described below:

(A) CK (or CK-MB) from index MI had not yet reached its maximum level: Recurrent thoracic chest pain or ischemia equivalent >20 minutes (or new ECG changes consistent with MI) and biomarker data:

1) A rise in CK within 24 hours of the event >2*URL (confirmed by either CK-MB or troponin > 1*URL) and ≥ 50% above the previous level or,

2) in absence of CK: a (post PCI) rise in CK-MB within 24 hours of the event >3*URL and ≥ 50% above the previous level, or

3) in absence of CK and CK-MB: a (post PCI) rise of troponin within 24 hours of the index event >3*URL and ≥ 50% above the previous level.

(B) Elevated CK (or CK-MB) following the index MI had peaked AND CK level has returned < URL then any new rise in:

1) CK >2*URL (confirmed by either CK-MB >URL or troponin >URL), or

2) in the absence of CK a rise of CK-MB >3*URL, or

3) in the absence of CK and CK-MB, a troponin rise >3*URL.

(C) CK (or CK-MB) following the index MI had peaked AND CK level has NOT returned <URL:

1) a rise in CK ≥ 50% above the previous level and >2 URL confirmed by either CK-MB >URL or troponin >URL, or

2) in absence of CK, when CK-MB has NOT returned to <URL, a rise in CK-MB ≥ 50% above the previous level and > 3 URL, or

3) in absence of CK, when CK-MB and troponin had not returned to <URL a rise in troponin ≥ 50% above the previous level and >3*URL.

Table S1. Status of follow-up at 1 year after PCI.

	All patients n = 1,830	No cessation N = 1,578	Crossover n = 131	Discontinuation n = 67	Disruption n = 54
Outcome at 1 year					
Alive: follow-up performed	1,793 (98.0%)	1,549 (98.2%)	130 (99.2%)	64(97%)	50 (90.7%)
Alive: refuses follow-up	1 (0.1%)	1 (0.1%)	0 (0%)	0 (0%)	0 (0%)
Alive: follow-up not performed	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Patient dead	34 (1.9%)	26 (1.6%)	1 (0.8%)	2 (3%)	5 (9.3%)
Untraceable	2 (0.1%)	2 (0.1%)	0 (0%)	0 (0%)	0 (0%)

Table S2. Medications at discharge and 1 year after PCI.

	Overall n = 1,830	No cessation n = 1,578	Crossover n = 131	Discontinuation n = 67	Disruption n = 54	p Values (vs. No cessation)		
						Crossover	Discontinuation	Disruption
At discharge, n (%)								
Acetylsalicylic acid	1828 (99.9)	1576 (99.9)	131 (100)	67 (100)	54 (100)	1.00	1.00	1.00
Prasugrel	1830 (100)	1578 (100)	131 (100)	67 (100)	54 (100)			
Oral anticoagulation	29 (1.6)	23 (1.5)	1 (0.8)	4 (6)	1 (1.9)	1.00	0.02	0.56
B-blocker	1574 (86.1)	1370 (86.9)	101 (77.1)	61 (91)	42 (77.8)	0.004	0.46	0.07
ACE inhibitor / ARB	1552 (84.9)	1337 (84.8)	109 (83.2)	60 (89.6)	46 (85.2)	0.61	0.38	1.00
Statin	1793 (98.0)	1546 (98.0)	129 (98.5)	65 (97)	53 (98.1)	1.00	0.39	1.00
At 1 year, n (%)								
Acetylsalicylic acid	1755/1791 (98.0)	1528/1547 (98.8)	123 (94.6)	62/65 (95.4)	42/49 (85.7)	0.003	0.06	<0.001
Prasugrel*	1477/1791 (82.5)	1458/1547 (94.2)	7 (5.4)	7/65 (10.8)	5/49 (10.2)	<0.001	<0.001	<0.001
Clopidogrel*	167/1791 (9.3)	53/1547 (3.4)	108 (83.1)	1/65 (1.5)	5/49 (10.2)	<0.001	0.72	0.03
Ticagrelor*	13/1791 (0.7)	2/1547 (0.1)	11/130 (8.5)	0/65 (0)	0/49 (0)	<0.001	1.000	1.000
Any dual antiplatelet therapy*	1617/1791 (90.3)	1484/1547 (95.9)	118/130 (90.8)	8/65 (12.3)	7/49 (14.3)	0.013	<0.001	<0.001
Oral anticoagulation	58/1790 (3.2)	23/1546 (1.5)	14/130 (10.8)	18/65 (27.7)	3/49 (6.1)	<0.001	<0.001	0.04
B-blocker	1473/1789 (82.3)	1293/1546 (83.6)	104/130 (80.0)	50/64 (78.1)	26/49 (53.1)	0.27	0.23	<0.001
ACE inhibitor / ARB	1135/1788 (63.5)	1011/1545 (65.4)	73 (56.2)	36/64 (56.3)	15/49 (30.6)	0.04	0.14	<0.001
Statin	1666/1788 (93.2)	1456/1545 (94.2)	123/130 (94.6)	58/64 (90.6)	29/49 (59.2)	1.00	0.27	<0.001

*330 days or more was accepted as compliant.

ACE indicates angiotensin converting enzyme; ARB, angiotensin receptor blocker.

Table S3. Baseline sociodemographic characteristics.

	Overall	No cessation	Crossover	Discontinuation	Disruption	p Value (vs. No cessation)		
	n = 1,830	n = 1,578	n = 131	n = 67	n = 54	Crossover	Discontinuation	Disruption
Professional situation	n = 638	n = 544	n = 51	n = 24	n = 19	0.13	0.07	0.38
Full time	339 (53.1)	298 (54.8)	21 (41.2)	8 (33.3)	12 (63.2)	0.08	0.06	0.64
Part time	64 (10.0)	54 (9.9)	5 (9.8)	2 (8.3)	3 (15.8)	1.00	1.00	0.43
No employment/retired	235 (36.8)	192 (35.3)	25 (49.0)	14 (58.3)	4 (21.1)	0.07	0.03	0.23
Education level	n = 599	n = 516	n = 44	n = 21	n = 18	0.72	0.95	0.96
Low education level	86 (14.4)	77 (14.9)	4 (9.1)	3 (14.3)	2 (11.1)	0.37	1.00	1.00
Appreticeship / vocational school	371 (61.9)	316 (61.2)	30 (68.2)	13 (61.9)	12 (66.7)	0.42	1.00	0.81
High school	67 (11.2)	57 (11.0)	5 (11.4)	3 (14.3)	2 (11.1)	1.00	0.72	1.00
University	75 (12.5)	66 (12.8)	5 (11.4)	2 (9.5)	2 (11.1)	1.00	1.00	1.00
Marital status	n = 671	n = 570	n = 54	n = 26	n = 21	0.98	0.73	0.05
Married	458 (68.3)	392 (68.8)	38 (70.4)	16 (61.5)	12 (57.1)	0.88	0.52	0.34
Divorced	96 (14.3)	80 (14.0)	8 (14.8)	3 (11.5)	5 (23.8)	0.84	1.00	0.21
Widowed	25 (3.7)	21 (3.7)	2 (3.7)	2 (7.7)	0 (0)	1.00	0.26	1.00
Single	68 (10.1)	58 (10.2)	5 (9.3)	4 (15.4)	1 (4.8)	1.00	0.33	0.71
Partnership	24 (3.6)	19 (3.3)	1 (1.9)	1 (3.8)	3 (14.3)	1.00	0.60	0.04
Living arrangement	n = 657	n = 560	n = 52	n = 25	n = 20	0.65	0.86	0.69
Living alone	123 (18.7)	104 (18.6)	11 (21.2)	5 (20)	3 (15)	0.71	0.80	1.00
Living with someone	534 (81.3)	456 (81.4)	41 (78.8)	20 (80)	17 (85)	0.71	0.80	1.00

Data only available for patients included in the SPUM-ACS registry.

Table S4. Univariable predictors of any prasugrel cessation.

	Sample size	Hazard ratio (95% CI)	p Value
Age (per 10 years)	n = 1830	1.18 (1.05-1.32)	0.005
Female sex	n = 1830	1.80 (1.35-2.38)	<0.001
Body mass index (per 10 units)	n = 1765	0.69 (0.50-0.96)	0.03
Diabetes mellitus	n = 1826	0.67 (0.44-1.03)	0.07
History of cerebrovascular accident	n = 1826	3.26 (1.34-7.89)	0.009
Clinically relevant valvular disease	n = 1161	3.78 (0.94-15.24)	0.06
Previous CABG	n = 1826	0.24 (0.03-1.73)	0.16
Time from symptom onset to balloon inflation >24h	n = 1811	1.37 (0.93-2.01)	0.11
Resuscitation before hospital arrival	n = 1161	0.19 (0.03-1.34)	0.09
LVEF (per 10%)	n = 1625	0.91 (0.81-1.02)	0.11
COPD	n = 1826	1.57 (0.81-3.05)	0.18
Multivessel treatment	n = 1826	1.31 (0.92-1.88)	0.13
Long lesion (any total stent length ≥20mm)	n = 1220	1.26 (0.89-1.78)	0.19
SYNTAX MI score	n = 479	1.29 (0.95-1.76)	0.11

CABG indicates coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction.

Table S5. Summary of individual primary-endpoint events following early prasugrel cessation.

Age (years)	Sex	Time from baseline to cessation (days)	Time from cessation to event (days)	Clinical event
I. Crossover				
48	Female	4	4	Patient changed from prasugrel to clopidogrel due to CABG operation. A cerebrovascular event occurred before the operation, 4 days after change to clopidogrel.
62	Male	35	7	Patient changed from prasugrel to clopidogrel 4 days prior to elective CABG surgery. A cerebrovascular event occurred 3 days after CABG surgery.
43	Female	98	8	Patient changed from prasugrel to clopidogrel because of menorrhagia. A non-Q-Wave myocardial infarction requiring PCI occurred after 8 days.
60	Male	15	10	Patient changed from prasugrel to clopidogrel due to CABG operation, during which the patient suffered a cerebrovascular event.
86	Male	302	42	Patient changed from prasugrel to clopidogrel due to a rib fracture with BARC 2 bleeding. A cerebrovascular event occurred 6 weeks thereafter.
56	Male	9	142	Patient changed from prasugrel to clopidogrel because of initiation of oral anticoagulation. Patient died suddenly (cardiac death, exact cause unknown).
80	Male	29	314	Patient changed from prasugrel to clopidogrel due to financial reasons. A non-Q-Wave myocardial infarction and TIA occurred after 314 days.
II. Discontinuation				
80	Male	185	4	Prasugrel was stopped prior to elective CABG operation, during which the patient suffered a myocardial infarction.
45	Male	216	9	Prasugrel was stopped because patient received palliative treatment due to metastatic lung cancer. Patient died 9 days later.
69	Male	265	61	Patient stopped prasugrel because of initiation of oral anticoagulation due to a pulmonary embolism. A stroke occurred 2 months thereafter.
71	Male	163	104	Prasugrel was stopped because of initiation of oral anticoagulation >5 months after index event. Patient died suddenly (cardiac death, exact cause unknown).
III. Disruption				
66	Male	23	5	Patient decided to stop prasugrel. Myocardial infarction due to stent thrombosis occurred after 5 days.

53	Male	22	7	Patient stopped taking prasugrel (personal decision) early after discharge and had a myocardial infarction 1 week later.
59	Female	68	7	Patient stopped prasugrel because of financial reasons and had a stent thrombosis 1 week later.
55	Female	82	10	Patient stopped prasugrel due to financial reasons early after discharge. Myocardial infarction due to stent thrombosis occurred after 10 days.
50	Male	195	132	Patient stopped prasugrel on own initiative and had a stent thrombosis 4 months later.
84	Male	24	235	Patient stopped prasugrel due to perceived side effect (gastric intolerance). Sudden cardiac death occurred after >7 months.

Table S6. Baseline clinical characteristics in patients enrolled in the COMFORTABLE AMI randomized trial vs. the observational registries (Bern PCI Registry and SPUM-ACS study).

	Randomized trial n=484	Observational registries n=1,346	p Value
Age	59.2 ± 10.7	59.2 ± 11.0	0.98
BMI	27.5 ± 4.1	27.3 ± 4.3	0.36
Current smoking	227 (47.1%)	635 (48.0%)	0.75
Hyperlipiemia	263 (54.9%)	672 (50.3%)	0.09
Hypertension	223 (46.1%)	617 (46.0%)	1.00
Diabetes mellitus	63 (13.0%)	172 (12.8%)	0.94
Family history of CAD	118 (24.6%)	344 (25.9%)	0.58
Renal dysfunction*	36 (7.7%)	99 (8.6%)	0.62
Renal insufficiency requiring dialysis	0 (0.0%)	3 (0.2%)	0.57
Peripheral artery disease	5 (1.0%)	33 (2.5%)	0.07
History of cerebrovascular accident	3 (0.6%)	11 (0.8%)	1.00
Previous PCI	22 (4.5%)	129 (9.6%)	<0.001
Previous CABG	9 (1.9%)	19 (1.4%)	0.52
Time from symptom onset to balloon inflation (min)	237 (161; 412)	225 (155; 390)	0.094
Killip class IV at presentation	3 (0.6%)	84 (6.3%)	<0.001
History of gastrointestinal bleeding	3 (0.6%)	10 (0.7%)	1.00
History of malignancy	16 (3.3%)	64 (4.8%)	0.20

Data are summarized as mean ± standard deviation, median (25%-75% interquartile range) or count (%).

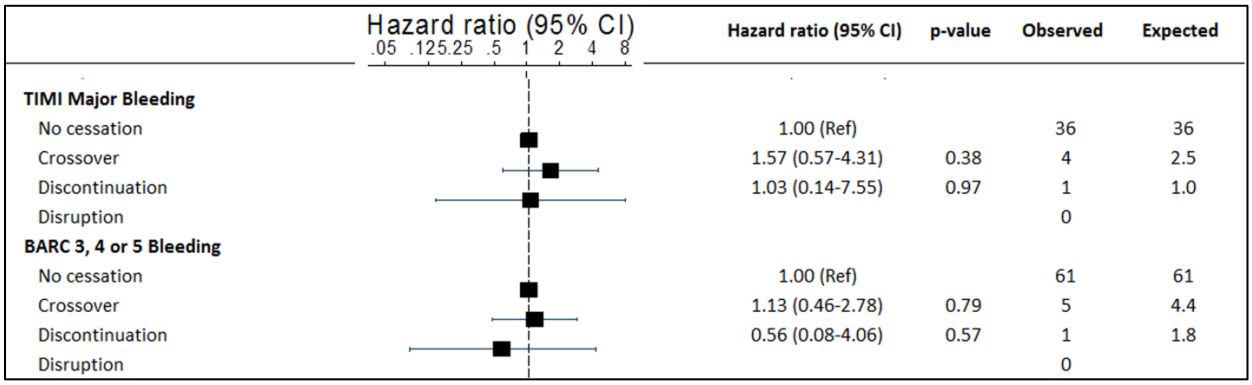
*Defined as estimated glomerular filtration rate <60 ml/min/1,73m² using the Cockcroft-Gault formula.

BMI indicates body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.

Table S7. Frequency of crossover, discontinuation and disruption of prasugrel in patients enrolled in the COMFORTABLE AMI randomized trial vs. the observational registries (Bern PCI Registry and SPUM-ACS study).

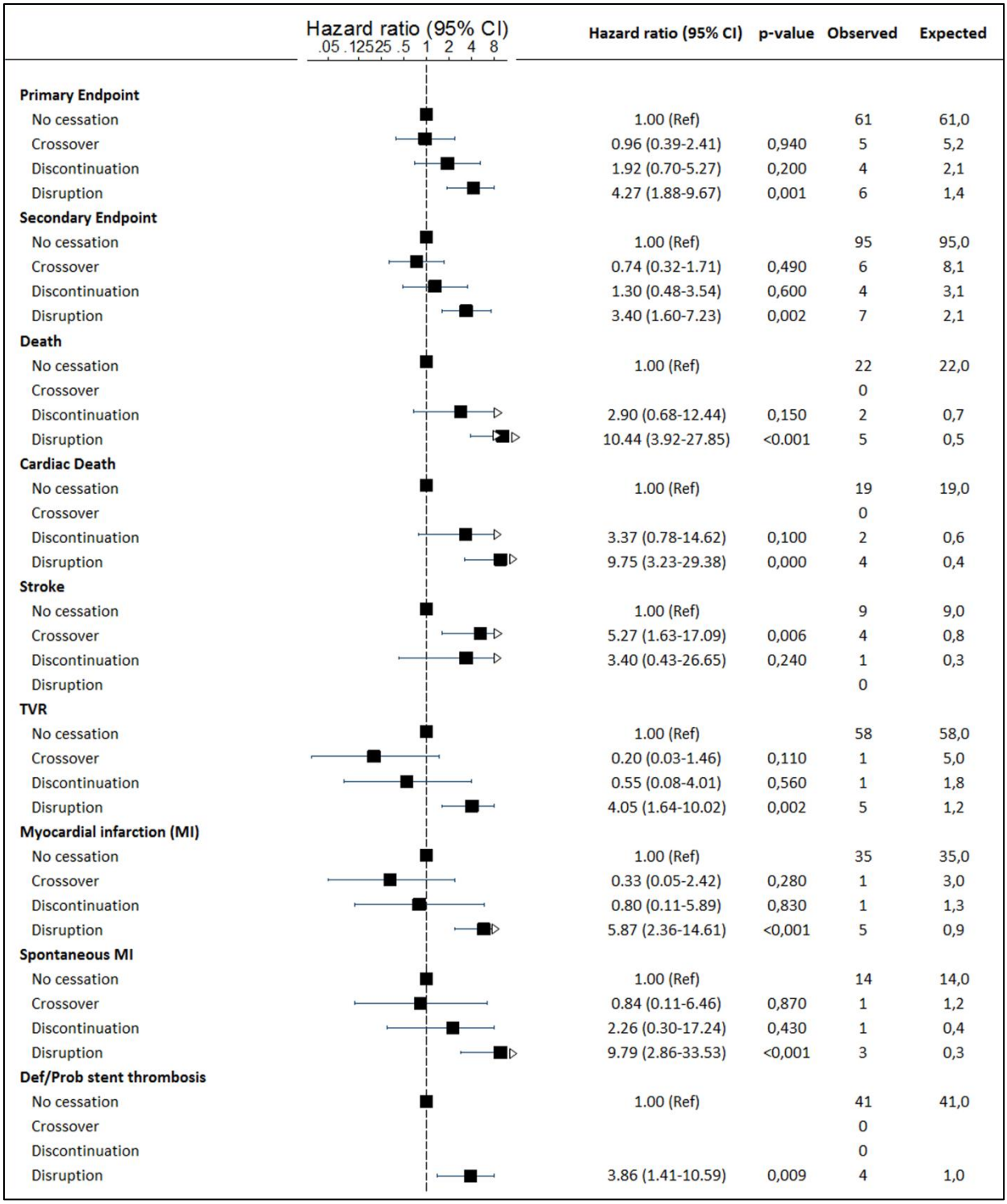
	Overall N=1,830	Randomized trial n=484	Registries n=1,346	p Value
No cessation	1578 (86.2%)	428 (88.4%)	1,150 (85.4%)	0.23
Crossover	131 (7.2%)	24 (5.0%)	107 (7.9%)	0.09
Discontinuation	67 (3.7%)	14 (2.9%)	53 (3.9%)	0.57
Disruption	54 (3.0%)	18 (3.7%)	36 (2.7%)	0.33

Figure S1. **Risk of bleeding in relation to early prasugrel cessation: crossover (n=131); discontinuation (n=67); and disruption (n=54).** Presented are numbers of observed events (from Kaplan-Meier estimate), expected events, hazard ratios and respective 95% confidence intervals (CI).



	Hazard ratio (95% CI)	p-value	Observed	Expected
TIMI Major Bleeding				
No cessation	1.00 (Ref)		36	36
Crossover	1.57 (0.57-4.31)	0.38	4	2.5
Discontinuation	1.03 (0.14-7.55)	0.97	1	1.0
Disruption			0	
BARC 3, 4 or 5 Bleeding				
No cessation	1.00 (Ref)		61	61
Crossover	1.13 (0.46-2.78)	0.79	5	4.4
Discontinuation	0.56 (0.08-4.06)	0.57	1	1.8
Disruption			0	

Figure S2. Results of time-dependent Cox model analyses for the risk of adverse clinical outcomes following early prasugrel cessation (crossover: n=107; discontinuation; n=53; disruption: n=36) in a sensitivity analysis including only patients enrolled in the observational registries (Bern PCI Registry and SPUM-ACS study; n=1,346). Presented are numbers of observed events (from Kaplan-Meier estimate), expected events, hazard ratios (HRs) and respective 95% confidence intervals (CI). The observed versus expected number of events are presented for each period, where expected numbers were calculated as number of events divided by the HR (compared to the reference of being on prasugrel treatment).



	Hazard ratio (95% CI)	p-value	Observed	Expected
Primary Endpoint				
No cessation	1.00 (Ref)		61	61,0
Crossover	0.96 (0.39-2.41)	0,940	5	5,2
Discontinuation	1.92 (0.70-5.27)	0,200	4	2,1
Disruption	4.27 (1.88-9.67)	0,001	6	1,4
Secondary Endpoint				
No cessation	1.00 (Ref)		95	95,0
Crossover	0.74 (0.32-1.71)	0,490	6	8,1
Discontinuation	1.30 (0.48-3.54)	0,600	4	3,1
Disruption	3.40 (1.60-7.23)	0,002	7	2,1
Death				
No cessation	1.00 (Ref)		22	22,0
Crossover			0	
Discontinuation	2.90 (0.68-12.44)	0,150	2	0,7
Disruption	10.44 (3.92-27.85)	<0.001	5	0,5
Cardiac Death				
No cessation	1.00 (Ref)		19	19,0
Crossover			0	
Discontinuation	3.37 (0.78-14.62)	0,100	2	0,6
Disruption	9.75 (3.23-29.38)	0,000	4	0,4
Stroke				
No cessation	1.00 (Ref)		9	9,0
Crossover	5.27 (1.63-17.09)	0,006	4	0,8
Discontinuation	3.40 (0.43-26.65)	0,240	1	0,3
Disruption			0	
TVR				
No cessation	1.00 (Ref)		58	58,0
Crossover	0.20 (0.03-1.46)	0,110	1	5,0
Discontinuation	0.55 (0.08-4.01)	0,560	1	1,8
Disruption	4.05 (1.64-10.02)	0,002	5	1,2
Myocardial infarction (MI)				
No cessation	1.00 (Ref)		35	35,0
Crossover	0.33 (0.05-2.42)	0,280	1	3,0
Discontinuation	0.80 (0.11-5.89)	0,830	1	1,3
Disruption	5.87 (2.36-14.61)	<0,001	5	0,9
Spontaneous MI				
No cessation	1.00 (Ref)		14	14,0
Crossover	0.84 (0.11-6.46)	0,870	1	1,2
Discontinuation	2.26 (0.30-17.24)	0,430	1	0,4
Disruption	9.79 (2.86-33.53)	<0,001	3	0,3
Def/Prob stent thrombosis				
No cessation	1.00 (Ref)		41	41,0
Crossover			0	
Discontinuation			0	
Disruption	3.86 (1.41-10.59)	0,009	4	1,0

Supplemental References:

1. Koskinas KC, Räber L, Zanchin T, Wenaweser P, Stortecky S, Moschovitis A, Khattab AA, Pilgrim T, Blöchlinger S, Moro C, Jüni P, Meier B, Heg D, Windecker S. Clinical impact of gastrointestinal bleeding in patients undergoing percutaneous coronary interventions. *Circ Cardiovasc Interv*. 2015;8:e002053.
2. Koskinas KC, Räber L, Zanchin T, Pilgrim T, Stortecky S, Hunziker L, Blöchlinger S, Billinger M, Gartwyl F, Moro C, Moschovitis A, Jüni P, Heg D, Windecker S. Duration of triple antithrombotic therapy and outcomes among patients undergoing percutaneous coronary intervention. *JACC Cardiovasc Interv*. 2016;9:1473-1483.
3. Zanchin T, Räber L, Koskinas KC, Piccolo R, Jüni P, Pilgrim T, Stortecky S, Khattab AA, Wenaweser P, Bloechlinger S, Moschovitis A, Frenk A, Moro C, Meier B, Fiedler GM, Heg D, Windecker S. Preprocedural High-Sensitivity Cardiac Troponin T and Clinical Outcomes in Patients With Stable Coronary Artery Disease Undergoing Elective Percutaneous Coronary Intervention. *Circ Cardiovasc Interv*. 2016;9:e003202.
4. Räber L, Klingenberg R, Heg D, Kelbæk H, Roffi M, Tüller D, Baumbach A, Zanchin T, Carballo D, Ostojic M, Stefanini GG, Rodondi N, von Birgelen C, Moschovitis A, Engstrøm T, Gencer B, Auer R, Meier B, Mach F, Lüscher TF, Jüni P, Matter CM, Windecker S; COMFORTABLE and SPUM-ACS Trial Investigators. Safety of Prasugrel Loading Doses in Patients Pre-Loaded With Clopidogrel in the Setting of Primary Percutaneous Coronary Intervention: Results of a Nonrandomized Observational Study. *JACC Cardiovasc Interv*. 2015;8:1064-1074.
5. Klingenberg R, Heg D, Räber L, Carballo D, Nanchen D, Gencer B, Auer R, Jaguszewski M, Stähli BE, Jakob P, Templin C, Stefanini GG, Meier B, Vogt P, Roffi M, Maier W, Landmesser U, Rodondi N, Mach F, Windecker S, Jüni P, Lüscher TF, Matter CM. Safety profile of prasugrel and clopidogrel in patients with acute coronary syndromes in Switzerland. *Heart.* 2015;101:854-863.
6. Räber L, Kelbaek H, Ostojic M, Baumbach A, Heg D, Tüller D, von Birgelen C, Roffi M, Moschovitis A, Khattab AA, Wenaweser P, Bonvini R, Pedrazzini G, Kornowski R, Weber K, Trelle S, Lüscher TF, Taniwaki M, Matter CM, Meier B, Jüni P, Windecker S. Effect of biolimus-eluting stents with biodegradable polymer vs bare-metal stents on cardiovascular events among patients with acute myocardial infarction: the COMFORTABLE AMI randomized trial. *JAMA.* 2012;308:777-787.
7. Räber L, Kelbaek H, Ostoijc M, Baumbach A, Tüller D, von Birgelen C, Roffi M, Pedrazzini G, Kornowski R, Weber K, Heg D, Matter C, Lüscher T, Taniwaki M, Meier B, Jüni P, Windecker S. Comparison of biolimus eluted from an erodible stent coating with bare metal stents in acute ST-elevation myocardial infarction (COMFORTABLE AMI trial): rationale and design. *EuroIntervention.* 2012;7:1435-1443.

Incidence, Predictors, and Clinical Impact of Early Prasugrel Cessation in Patients With ST–Elevation Myocardial Infarction

Konstantinos C. Koskinas, Thomas Zanchin, Roland Klingenberg, Baris Gencer, Fabrice Temperli, Andreas Baumbach, Marco Roffi, Aris Moschovitis, Oliver Muller, David Tüller, Stefan Stortecky, Francois Mach, Thomas F. Lüscher, Christian M. Matter, Thomas Pilgrim, Dik Heg, Stephan Windecker and Lorenz Räber

J Am Heart Assoc. 2018;7:e008085; originally published April 13, 2018;
doi: 10.1161/JAHA.117.008085
The *Journal of the American Heart Association* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Online ISSN: 2047-9980